

VERIFICATION OF A TRANSLATION

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My name and post office address are as stated below;

That I am knowledgeable in the English language and in the language in which the below identified application was filed, and that I believe the English translation of International Application No. PCT/JP00/05743 is a true and complete translation of the above-identified International Application as filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated this 18th day of February, 2002

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SPECIFICATION

2 α -SUBSTITUTED VITAMIN D DERIVATIVES

5 TECHNICAL FIELD

The present invention relates to novel vitamin D derivatives, more particularly, relates to vitamin D derivatives having a substituent at the 2 α -position.

10 BACKGROUND ART

Active vitamins D₃ including 1 α ,25-dihydroxyvitamin D₃ are known to exhibit a variety of physiological activities such as calcium metabolism regulatory activities, growth inhibitory and differentiation toward tumor cells, and immunoregulatory activities. However, some active vitamins D₃ disadvantageously may cause hypercalcemia during long-term and continuous administration, and are thus not suitable for use as antitumor agents, antirheumatic agents, or the like. Thus, a number of synthetic studies have been conducted for the purpose of obtaining vitamin D derivatives which are superior in certain activities.

The studies conducted by the inventors of the present invention revealed that 2 α -methyl derivatives of active vitamin D₃, i.e., 1 α ,25-dihydroxyvitamin D₃, increases binding property to vitamin D receptor (VDR) (K.Konno, et al., Bioorg. Med. Chem. Lett., 1998, 8, 151). Furthermore, a combination of the 2 α -methylation and epimerization at the 20-position on the side chain has been reported to

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additionally enhance the binding property to VDR
(T.Fujishima et al., Bioorg. Med. Chem. Lett., 1998, 8,
2145).

However, no work has been done to synthesize a
5 vitamin D derivative, in which the 2-position is
substituted, other than with a methyl group, and the groups
at the 20-position are epimerized; further, the
physiological activities of such a vitamin D derivative
have not been studied.

10

DISCLOSURE OF THE INVENTION

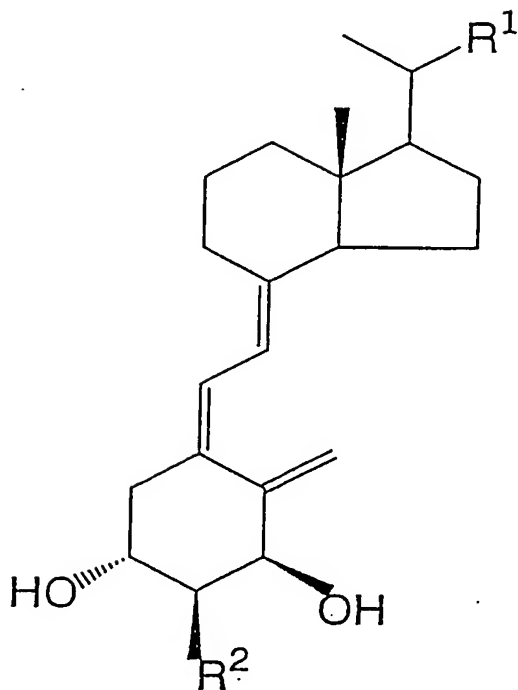
An object of the present invention is to synthesize
and provide a novel vitamin D₃ derivative, in which the
2-position is substituted, other than with a methyl group,
15 the hydroxy groups at 1- and 3-positions are α - and β -
oriented, respectively, and the groups at the 20-position
are epimerized.

Another object of the present invention is to
evaluate bioavailability of the synthesized vitamin D₃
20 derivative.

As a result of careful studies to achieve the above
objects, the inventors of the present invention have
succeeded in synthesizing vitamin D derivatives having a
variety of configurations by synthesizing CD-ring compounds
25 each having a desired side chain portion and then coupling
it with A-ring compounds each having a desired group at the
2 α -position, thereby completing the present invention.

According to an aspect of the present invention, a

vitamin D derivative represented by Formula (I) is provided:



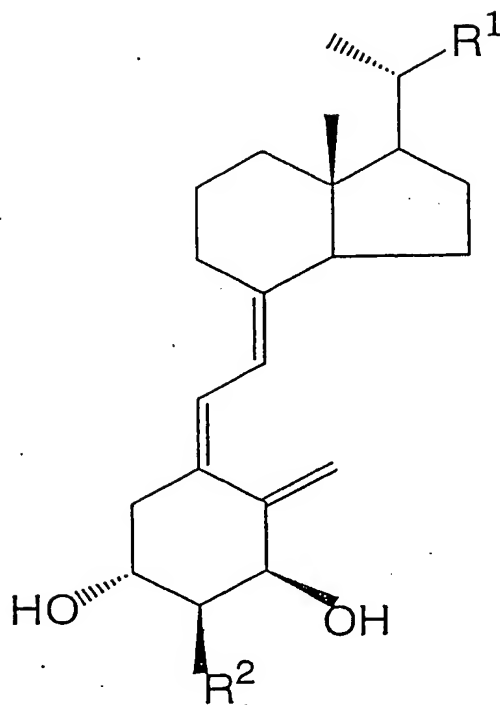
wherein

R^1 represents a saturated aliphatic C_{1-15} hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic C_{1-10} hydrocarbon group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1 hydrocarbon group, R^2 is substituted with at least one substituent.

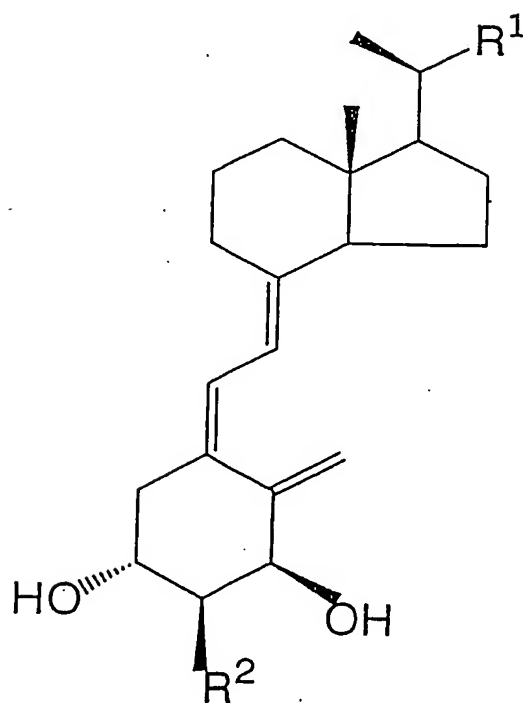
Among such vitamin D derivatives, those represented

by the following Formula (II) or



(II)

(III) are preferred.



(III)

In Formulae (I), (II) and (III), R² is preferably a hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethyl, propyl, butyl, pentyl or hexyl group.

5 In Formulae (I), (II) and (III), R¹ is preferably a saturated aliphatic C₁₋₁₅ hydrocarbon group substituted with one hydroxy or protected hydroxy group, more preferably R¹ is a 4-hydroxy-4-methylpentyl group.

10 Particularly preferred compounds of the present invention are those selected from the group consisting of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(4'-hydroxybutyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(5'-hydroxypentyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(6'-hydroxyhexyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-pentyl-1,3,25-triol and (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hexyl-1,3,25-triol.

According to the present invention, a pharmaceutical composition comprising the above mentioned vitamin D derivative as an active ingredient is provided. Examples of such medicaments include therapeutic agents for diseases accompanied with abnormal calcium metabolism, an antitumor agent, an immunomodulator, and the like.

According to the present invention, use of the above mentioned vitamin D derivative for a medicament is provided. Examples of such medicaments include therapeutic agents for diseases accompanied with abnormal calcium metabolism, an antitumor agent, an immunomodulator, and the like.

PREFERRED MODE FOR CARRYING OUT THE INVENTION

Detailed modes and methods with respect to vitamin D derivatives represented by Formula (I) and pharmaceutical compositions including the vitamin D derivatives in accordance with the present invention are described in further detail below.

The contents of the specification of Japanese Patent Application No.11-241650, the application on the basis of which the present application claims priority are to be incorporated in their entirety by reference.

In Formula (I), R^1 represents a saturated aliphatic C_{1-15} hydrocarbon group which may be substituted with 1 to 3 hydroxy groups or protected hydroxy groups.

In the present application, a saturated aliphatic hydrocarbon group generally means a straight or branched

alkyl group. Specific examples thereof include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl and tert-butyl groups, and further include pentyl, hexyl, heptyl, octyl, nonyl and decanyl groups. Among them, 3-methylbutyl, 3-ethylpentyl, 4-methylpentyl, 3-(n-propyl)hexyl, 4-ethylhexyl, 5-methylhexyl, 6-methylheptyl, 5-ethylheptyl and 4-(n-propyl)hepty groups are preferred.

R^1 is preferably a 5-methylhexyl, 4-ethylhexyl or 4-methylpentyl group.

The saturated aliphatic hydrocarbon groups optionally substituted with hydroxy groups means that any hydrogen atoms in the above mentioned saturated hydrocarbon groups may be substituted with one or more hydroxy groups.

In the definition of R^1 , the number of hydroxy substituents is 0, 1, 2 or 3, preferably 1 or 2, and more preferably 1. Specific examples of the saturated aliphatic hydrocarbon groups substituted with at least one hydroxy group include 2-hydroxy-2-methylpropyl, 3-hydroxy-2-methylpropyl, 2,3-dihydroxy-2-methylpropyl, 2-ethyl-2-hydroxybutyl, 2-ethyl-3-hydroxybutyl, 2-ethyl-2,3-dihydroxybutyl, 2-hydroxy-2-(n-propyl)pentyl, 3-hydroxy-2-(n-propyl)pentyl, 2,3-dihydroxy-2-(n-propyl)pentyl, 2-hydroxy-3-methylbutyl, 3-hydroxy-3-methylbutyl, 4-hydroxy-3-methylbutyl, 2,3-dihydroxy-3-methylbutyl, 2,4-dihydroxy-3-methylbutyl, 3,4-dihydroxy-3-methylbutyl, 3-ethyl-2-hydroxypentyl, 3-ethyl-3-hydroxypentyl, 3-ethyl-4-hydroxypentyl, 3-ethyl-2,3-dihydroxypentyl, 3-ethyl-2,4-dihydroxypentyl, 3-ethyl-3,4-dihydroxypentyl, 2-hydroxy-3-

(n-propyl)hexyl, 3-hydroxy-3-(n-propyl)hexyl, 4-hydroxy-3-(n-propyl)hexyl, 2,3-dihydroxy-3-(n-propyl)hexyl, 2,4-dihydroxy-3-(n-propyl)hexyl, 3,4-dihydroxy-3-(n-propyl)hexyl, 3-hydroxy-4-methylpentyl, 4-hydroxy-4-methylpentyl, 5-hydroxy-4-methylpentyl, 3,4-dihydroxy-4-methylpentyl, 3,5-dihydroxy-4-methylpentyl, 4,5-dihydroxy-4-methylpentyl, 4-ethyl-3-hydroxyhexyl, 4-ethyl-4-hydroxyhexyl, 4-ethyl-5-hydroxyhexyl, 4-ethyl-3,4-dihydroxyhexyl, 4-ethyl-3,5-dihydroxyhexyl, 4-ethyl-4,5-dihydroxyhexyl, 3-hydroxy-4-(n-propyl)heptyl, 4-hydroxy-4-(n-propyl)heptyl, 5-hydroxy-4-(n-propyl)heptyl, 3,4-dihydroxy-4-(n-propyl)heptyl, 3,5-dihydroxy-4-(n-propyl)heptyl, 4,5-dihydroxy-4-(n-propyl)heptyl, 4-hydroxy-5-methylhexyl, 5-hydroxy-5-methylhexyl, 6-hydroxy-5-methylhexyl, 4,5-dihydroxy-5-methylhexyl, 4,6-dihydroxy-5-methylhexyl, 5,6-dihydroxy-5-methylhexyl, 5-ethyl-4-hydroxyheptyl, 5-ethyl-5-hydroxyheptyl, 5-ethyl-6-hydroxyheptyl, 5-ethyl-4,5-dihydroxyheptyl, 5-ethyl-4,6-dihydroxyheptyl, 5-ethyl-5,6-dihydroxyheptyl, 4-hydroxy-5-(n-propyl)octyl, 5-hydroxy-5-(n-propyl)octyl, 6-hydroxy-5-(n-propyl)octyl, 4,5-dihydroxy-5-(n-propyl)octyl, 4,6-dihydroxy-5-(n-propyl)octyl, 5,6-dihydroxy-5-(n-propyl)octyl, 5-hydroxy-6-methylheptyl, 6-hydroxy-6-methylheptyl, 7-hydroxy-6-methylheptyl, 5,6-dihydroxy-6-methylheptyl, 5,7-dihydroxy-6-methylheptyl, 6,7-dihydroxy-6-methylheptyl, 6-ethyl-5-hydroxyoctyl, 6-ethyl-6-hydroxyoctyl, 6-ethyl-7-hydroxyoctyl, 6-ethyl-5,6-dihydroxyoctyl, 6-ethyl-5,7-dihydroxyoctyl, 6-ethyl-6,7-

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5 dihydroxyoctyl, 5-hydroxy-6-(n-propyl)nonyl, 6-hydroxy-6-(n-propyl)nonyl, 7-hydroxy-6-(n-propyl)nonyl, 5,6-dihydroxy-6-(n-propyl)nonyl, 5,7-dihydroxy-6-(n-propyl)nonyl and 6,7-dihydroxy-6-(n-propyl) groups. Among them, 4-hydroxy-4-methylpentyl, 4-ethyl-4-hydroxyhexyl, 5-hydroxy-5-methylhexyl and 5-ethyl-5-hydroxyheptyl groups are more preferred and a 4-hydroxy-4-methylpentyl group is further more preferred.

10 Examples of protecting groups for the hydroxy groups in R¹ of Formulae (I), (II) and (III) include acyl groups, substituted silyl groups and substituted alkyl groups, preferably acyl groups and substituted silyl groups.

15 Acyl groups mean substituted carbonyl groups; examples of the substituents of the carbonyl groups include a hydrogen atom, optionally substituted lower alkyl groups, optionally substituted aryl groups, optionally substituted lower alkyloxy groups, optionally substituted aryloxy groups, optionally substituted aralkyloxy groups and the like. Preferred examples of the acyl groups include a
20 formyl group, lower alkylcarbonyl groups, optionally substituted phenylcarbonyl groups, lower alkyloxycarbonyl groups, optionally substituted phenylalkyloxycarbonyl groups and the like, more preferred examples include formyl, acetyl, propionyl, butyryl, pivaloyl, benzoyl,
25 methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and benzyloxycarbonyl groups.

Substituted silyl groups mean silyl groups substituted with lower alkyl groups which may have one or

more substituents, optionally substituted aryl groups and the like. Preferably, substituted silyl groups mean tri-substituted silyl groups. Preferred examples of the substituted silyl groups include trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldiphenylsilyl and tert-butyldimethylsilyl groups.

Substituted alkyl groups mean those alkyl groups which are substituted with one or more substituents. Preferred examples of the substituents include optionally substituted alkyloxy groups and optionally substituted aryl groups, with optionally substituted alkyloxy groups being particularly preferred. Examples of the alkyl groups substituted with an optionally substituted alkyloxy group (such as an alkyloxy group) include, for example, methoxymethyl, 2-methoxyethoxymethyl and tetrahydropyran-2-yl groups. Examples of the substituents include halogen atoms and cyano, nitro, amino, hydroxy, alkyl, alkyloxy, acyloxy and sulfonyl groups and the like.

In Formulae (I), (II) and (III), R^2 represents a saturated aliphatic hydrocarbon group which may be substituted with one or more of substituents selected from the group consisting of a hydroxy group, halogen atoms, cyano, lower alkoxy, amino and acylamino groups.

Examples of the saturated aliphatic hydrocarbon groups include the above described straight or branched alkyl groups, preferably having 1-10 carbon atoms, more preferably 1-6 carbon atoms, and particularly preferably 3-5 carbon atoms.

The halogen atoms include fluorine, chlorine, bromine and iodine atoms, and the lower alkoxy groups mean those having 1-6 carbon atoms. The hydroxy and amino group may have protecting groups.

5 Similar to the above, preferred examples of the acyl groups of the acylamino group include a formyl group, lower alkylcarbonyl groups, optionally substituted phenylcarbonyl groups, lower alkyloxycarbonyl groups, optionally substituted phenylalkyloxycarbonyl groups and the like,
10 more preferably formyl, acetyl, propionyl, butyryl, pivaloyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and benzyloxycarbonyl groups.

 As the substituents, a hydroxy group and a halogen atom are preferred. The number of substituents is 0, 1, 2
15 or 3, preferably 1 or 2, and more preferably 1.

 It is particularly preferred that R² is a hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethyl, propyl, butyl, pentyl or hexyl group.

20 The stereochemistry of the hydroxy groups at the 1- and 3-positions and the methyl group at the 2-position in compounds of Formula (I) of the present invention can occur in α or β conformation, and the respective compounds are all included within the scope of the present invention.

25 Examples of the compounds of Formula (I) of the present invention include 1 α ,25-dihydroxy-2 α -hydroxymethylvitamin D₃, 1 α ,25-dihydroxy-2 α -hydroxyethylvitamin D₃, 1 α ,25-dihydroxy-2 α -

hydroxypropylvitamin D₃, 1α,25-dihydroxy-2α-hydroxybutylvitamin D₃, 1α,25-dihydroxy-2α-hydroxypentylvitamin D₃, 1α,25-dihydroxy-2α-hydroxyhexylvitamin D₃, 1α,25-dihydroxy-2α-ethylvitamin D₃,
5 1α,25-dihydroxy-2α-propylvitamin D₃, 1α,25-dihydroxy-2α-butylvitamin D₃, 1α,25-dihydroxy-2α-pentylvitamin D₃ and 1α,25-dihydroxy-2α-hexylvitamin D₃. Particularly preferred examples include (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-
10 5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(4'-hydroxybutyl)-1,3,25-triol, (5Z,7E)-
15 (1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(5'-hydroxypentyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(6'-hydroxyhexyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol, (5Z,7E)-
20 (1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-pentyl-1,3,25-triol and (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-
25 5,7,10(19)-cholestatriene-2-hexyl-1,3,25-triol.

Although there is no limitation with respect to methods for synthesizing the compounds represented by Formula (I) of the present invention, for example, A-ring

and CD-ring parts of a vitamin D derivative are separately synthesized and then subjected to coupling, as described in the following Examples.

CD-ring part compounds of the vitamin D derivatives
5 are known. A desired CD-ring compound can be obtained by appropriately modifying a side chain of a known CD-ring compound or can be obtained from a known CD-ring compound having a corresponding side chain.

These known vitamin D derivatives are disclosed in
10 Japanese Patent Publication (Kokai) Nos. 61-267550, 6-72994 and 6-256300, Japanese Patent Publication (Kohyo) Nos. 4-503669 and 4-504573, and Japanese Patent Publication (Kokai) No. 10-182597, WO 94/14766, WO 95/27697, and the like. After protecting the hydroxy group of the above
15 mentioned vitamin D derivative with a protecting group, the resultant compound is subjected to ozonolysis, and then, to NaBH_4 reduction, giving an alcohol having a hydroxy group at the 8-position. Oxidization using an appropriate
20 oxidant gives a ketone having an oxo group at the 8-position. A CD-ring compound having a desired side chain can be obtained by converting the oxo group at the 8-position with a bromomethylene group.

A-ring compounds having a substituent at the 2β -position are known and are described by K. Konno et al.
25 (Bioorg. Med. Chem. Lett., 8(1998) P.151-156) and T. Fujishima et al. (Bioorg. Med. Chem. Lett., 8(1998), P.2145-2148).

A-ring compounds having a substituent at the 2α -

position can be synthesized from a starting material, such as 1,2-O-isopropylidene- α -D-(R)-xylofuranose, according to the process described in the following Examples, however there is no limitation with respect to a method for synthesizing the compounds. Compounds other than those described in the following Examples can also be synthesized in the same manner by using corresponding starting materials.

Coupling of an A-ring compound with a CD-ring compound can be carried out using a known method. An A-ring compound, which is obtainable by the above method and which has a triple bond at one terminal and a double bond at the other terminal, is reacted with a CD-ring compound, which has a bromomethylene group at the coupling site for the A-ring compound, in the presence of a palladium catalyst such as $\text{Pd}_2(\text{dba})_3$ and triphenylphosphine (PPh_3) in an appropriate solvent.

After the coupling reaction, the resulting product is purified in a usual manner such as thin layer chromatography and subjected to removal of the hydroxy protecting group, to give a desired vitamin D derivative having a substituent at the 2α -position.

The compounds of the present invention are preferably formulated into appropriate dosage forms with pharmaceutically acceptable carriers, excipients, disintegrants, lubricants, binders, flavors, colorants and the like; examples of the dosage forms include tablets, granules, fine granules, capsules, powders, injections,

solutions, suspensions, emulsions, percutaneous administration formulations, suppositories and the like.

There is no restriction on routes of administration for the compounds of the present invention; the compounds
5 may be administered orally or parenterally (intravenously, intramuscularly, intraperitoneally, percutaneously and the like).

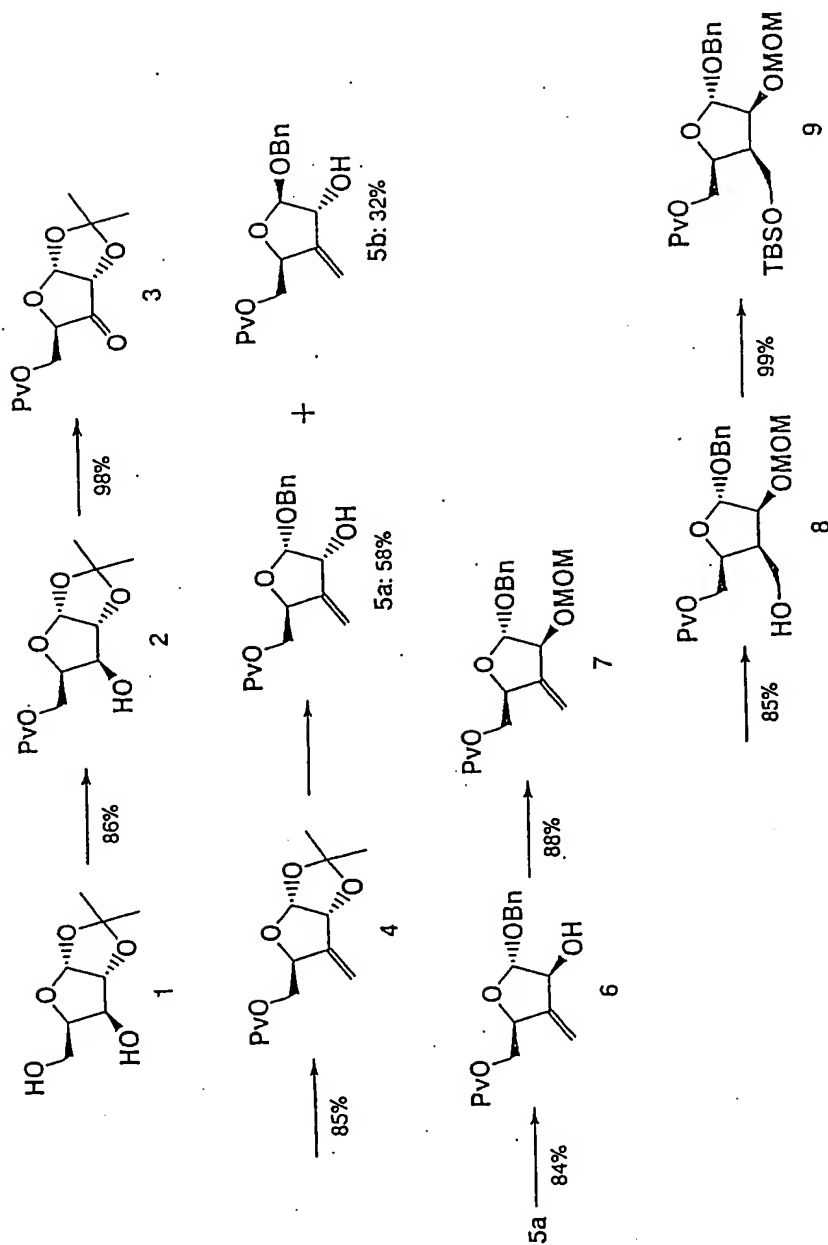
10 Dosage of compounds of the present invention can be appropriately chosen depending on target disease, conditions, body type, constitution, age and sex of the patient, administration route, dosage form and other factors. Typically, the lower limit for an adult ranges from 0.001 μg to 0.1 μg and preferably around 0.01 μg daily, and the upper limit for an adult ranges from 100 μg
15 to 10000 μg and preferably from 200 μg to 1000 μg daily, which may be administered at a time or in divided portions twice or three times a day.

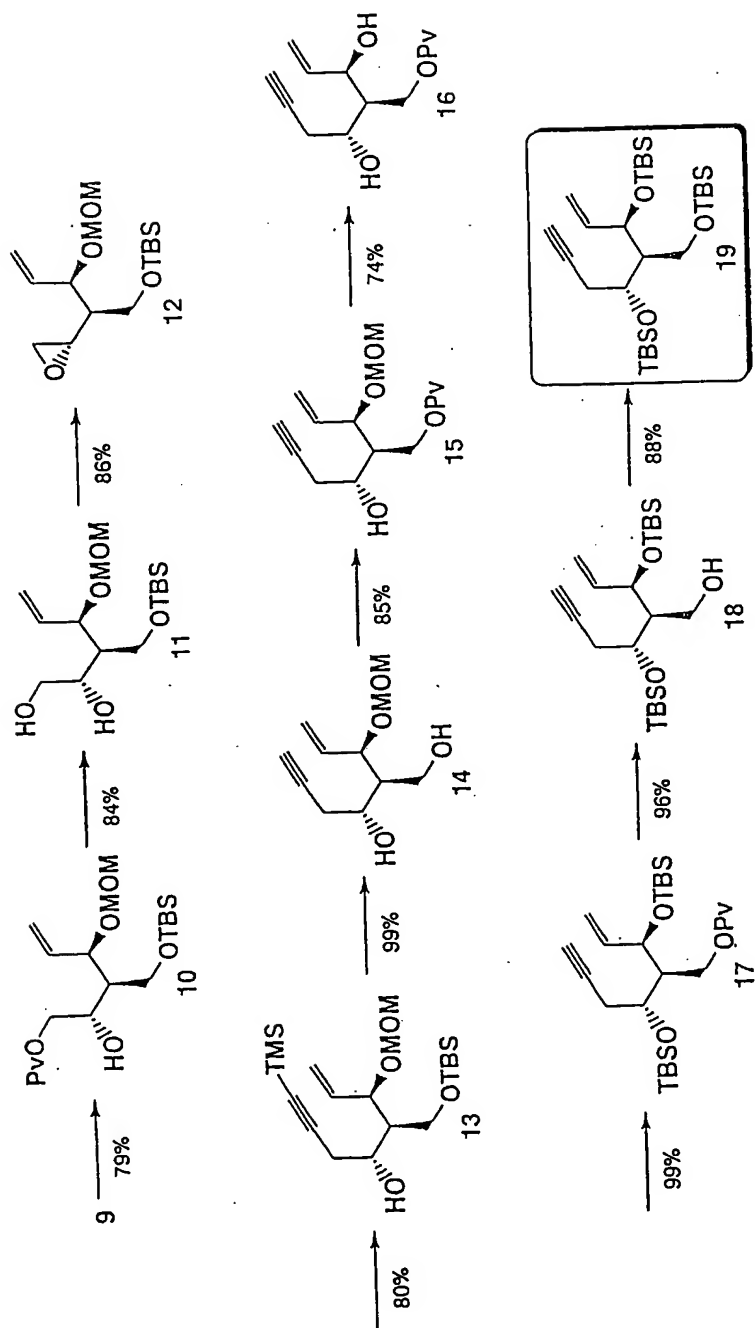
EXAMPLES

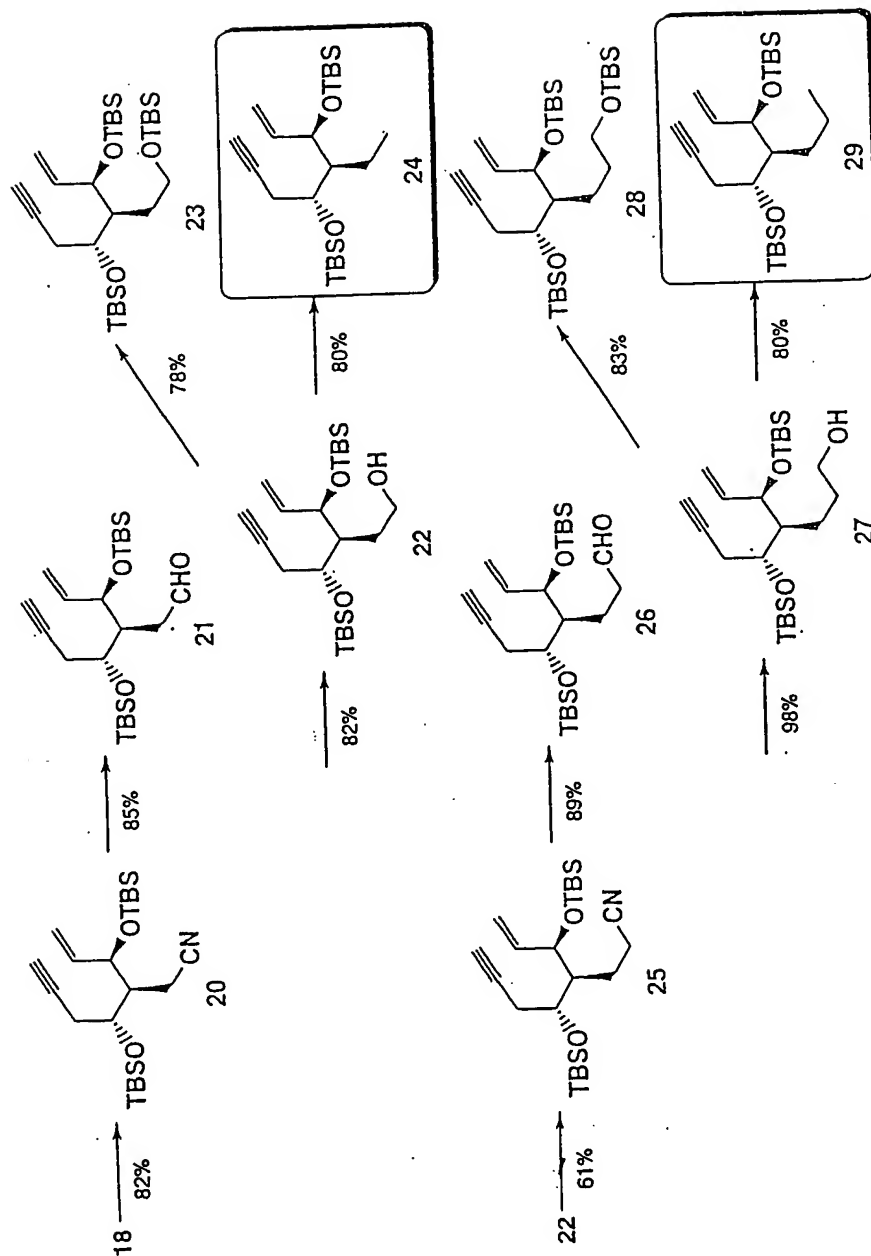
20 The present invention will be described specifically by way of the following Examples, which in no way limit the invention.

(Example 1): Synthesis of an A-ring compound used for the synthesis of a vitamin D derivative having a substituent at
25 the 2 α -position.

Example 1 was conducted according to the following reaction scheme:







(1) Synthesis of 5-O-pivaloyl-1,2-O-isopropylidene- α -D-xylofuranose (Compound 2)

1,2-O-isopropylidene- α -D-xylofuranose (Compound 1, 15.0 g, 78.9 mmol) was dissolved in pyridine (70 mL), cooled to 0°C under argon atmosphere, and trimethylacetyl chloride (9.9 g, 82.2 mmol) was added dropwise over 2 hours. The reaction mixture was stirred for 10 hours at that temperature, then MeOH (5 mL) was added and the mixture was concentrated. The residue was dissolved in diethyl ether (500 mL) and washed with water (100 mL), saturated aqueous copper sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL). The aqueous layer was extracted with 100 mL of diethyl ether three times. The ether layers were combined with the previously obtained diethyl ether layer. The ether layer thus obtained was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:4) to give Compound 2 (18.7 g, 86%) as a colorless oil.

$[\alpha]^{20}_D$ 2.69 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.22 (s, 9H), 1.32 (s, 3H), 1.51 (s, 3H), 4.10 (d, 1H, J = 2.8 Hz), 3.78 (bs, 1H), 4.17 (dd, 1H, J = 5.6, 11.2 Hz), 4.25 (ddd, 1H, J = 2.8, 5.6, 7.2 Hz), 4.50 (dd, 1H, J = 7.2, 11.2 Hz), 4.56 (d, 1H, J = 3.6 Hz), 5.93 (d, 1H, J = 3.6 Hz); HREIMS $\text{C}_{12}\text{H}_{19}\text{O}_6$ ($\text{M}^+ - \text{CH}_3$) calcd. 259.1182, found 259.1182.

(2) Synthesis of 5-O-pivaloyl-1,2-O-isopropylidene- α -D-erythro-3-pentofuranose (Compound 3)

Compound 2 (10.5 g, 38.3 mmol) was dissolved in

dichloromethane (800 mL), zeolite (75 g) and PCC (pyridinium chlorochromate) (36.5 g, 169.4 mmol) were added at room temperature and the mixture was stirred for 3 hours. The reaction mixture was diluted with hexane (800 mL), filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 2:3) to give ketone Compound 3 (10.2 g, 98%) as a colorless oil.

$[\alpha]^{20}_D$ 4.19 (c 1.13, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.18 (s, 9H), 1.44 (s, 3H), 1.48 (s, 3H), 4.23 (d, 1H, J = 3.2, 11.6 Hz), 4.37 (dd, 1H, J = 1.2, 3.2 Hz), 4.39 (dd, 1H, J = 3.2, 11.6 Hz), 4.57 (dt, 1H, J = 1.2, 3.2 Hz), 6.10 (d, 1H, J = 4.4 Hz); HREIMS $\text{C}_{13}\text{H}_{20}\text{O}_6$ (M^+) calcd. 276.1260, found 276.1262.

(3) Synthesis of 5-O-pivaloyl-1,2-O-isopropylidene-3-deoxy-3-C-methylene- α -D-xylo-pentofuranose (Compound 4)

Methyltriphenylphosphonium bromide (7.7 g, 21.6 mmol) was mixed with THF (100 mL), and 1.0M NaHMDS (sodium bis(trimethylsilyl)amide) in THF (18.0 mL, 18.0 mmol) was added dropwise at room temperature. The yellow reaction suspension was stirred for 1.5 hours at room temperature, cooled to -78°C under argon atmosphere, and Compound 3 (4.3 g, 15.8 mmol) was slowly added. The reaction mixture was stirred at that temperature for 30 min., then warmed to room temperature and stirred for further 1 hour. The reaction mixture was cooled to 0°C , then MeOH (10 mL) was added. The mixture was diluted with diethyl ether (200 mL), and washed with a saturated aqueous ammonium chloride solution (100 mL) and with saturated brine (100 mL), each

three times. The aqueous layer was extracted with 100 mL of diethyl ether three times and combined with the previously obtained ether layer. The ether layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give olefin Compound 4 (3.6 g, 85%) as a colorless oil.

$[\alpha]^{20}_D$ 13.45 (c 1.31, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.20 (s, 9H), 1.39 (s, 3H), 1.52 (s, 3H), 4.19 (dd, 1H, $J = 4.8, 12.0$ Hz), 4.23 (dd, 1H, $J = 3.6, 12.0$ Hz), 4.91 (dd, 1H, $J = 1.2, 4.0$ Hz), 4.94 (td, 1H, $J = 2.6, 3.4, 4.8$ Hz), 5.22 (t, 1H, $J = 1.2$ Hz), 5.48 (dd, 1H, $J = 1.2, 2.4$ Hz), 5.87 (d, 1H, $J = 4.0$ Hz); HREIMS $\text{C}_{13}\text{H}_{19}\text{O}_5$ ($\text{M}^+ - \text{Me}$) calcd. 255.1235, found 255.1232.

(4) Synthesis of benzyl 5-O-pivaloyl-3-deoxy-3-C-methylene- α -D-xylo-pentofuranose (Compound 5a) and benzyl 5-O-pivaloyl-3-deoxy-3-C-methylene- β -D-xylo-pentofuranose (Compound 5b)

Compound 4 (3.2 g, 11.9 mmol) and benzyl alcohol (8.0 g, 74.1 mmol) were dissolved in toluene (22 mL), cooled to 0°C , and 4.0M hydrogen chloride-dioxane solution (10 mL, 40.0 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 16 hours and diluted with a diethyl ether (200 mL). The diluted solution was cooled to 0°C and neutralized with saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was washed with water (50 mL) and with saturated brine (50 mL) each three times. The aqueous layer was extracted with

50 mL of diethyl ether three times, combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl

5 acetate/hexane 1:4) to give Compound 5a (2.2 g, 58%) and Compound 5b (1.22 g, 32%) as colorless oily alcohols.

5a: $[\alpha]^{20}_D$ 19.56 (c 1.23, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.20 (s, 9H), 2.26 (d, 1H, $J = 11.6$ Hz), 4.18 (dd, 1H, $J = 4.8, 12.0$ Hz), 4.60 (d, 1H, $J = 12.0$ Hz), 4.73 (ddt, 1H, $J = 2.4, 3.4, 4.8$ Hz), 4.81 (d, 1H, $J = 12.0$ Hz), 5.15 (d, 1H, $J = 4.4$ Hz), 5.18 (t, 1H, $J = 2.4$ Hz), 5.39 (t, 1H, $J = 2.4$ Hz), 7.34 (m, 5H). 5b: $[\alpha]^{20}_D$ -4.00 (c 1.07, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.27 (s, 9H), 2.61 (bs, 1H), 4.14 (dd, 1H, $J = 6.8, 12.0$ Hz), 4.19 (dd, 1H, $J = 4.8, 12.0$ Hz), 4.42 (t, 1H, $J = 1.2$ Hz), 4.49 (d, 1H, $J = 11.6$ Hz), 4.76 (d, 1H, $J = 11.6$ Hz), 4.89 (qt, 1H, $J = 1.2, 4.8, 6.2$ Hz), 5.03 (s, 1H), 5.26 (t, 1H, $J = 1.2$ Hz), 7.33 (m, 5H).

(5) Synthesis of benzyl 5-O-pivaloyl-3-deoxy-3-C-methylene- α -D-xylo-pentofuranoside (Compound 6)

20 Compound 5a (2.0 g, 6.25 mmol), p-nitrobenzoic acid (2.1 g, 12.6 mmol) and triphenylphosphine (3.3 g, 12.6 mmol) were dissolved in THF (40 mL), cooled to 0°C under argon atmosphere, and a 40% DEAD-toluene solution (5.8 g, 13.9 mmol) was added. The reaction mixture was stirred at
25 that temperature for 15 min., warmed to room temperature and stirred for further 3 hours. The reaction mixture was cooled to 0°C , then MeOH (10 mL) was added. The mixture was diluted with diethyl ether (100 mL) and washed with

saturated aqueous sodium bicarbonate solution (50 mL) and saturated brine (50 mL), each three times. The aqueous layer was extracted with 50 mL of diethyl ether three times, combined with the previously obtained ether layer.

5 The ether layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:10) to give a crude ester compound as a colorless oil, which was subjected to the next reaction without further purification.

10 The ester was dissolved in MeOH (100 mL), cooled to 0°C, and 1.0M aqueous sodium hydroxide solution (1.0 mL, 1.00 mmol) was added dropwise. The reaction mixture was stirred for 1 hour at the same temperature, neutralized by the addition of 1.0 M hydrochloric acid (1.5 mL, 1.5 mmol)
15 and concentrated. The residue was dissolved in diethyl ether (200 mL) and washed with a saturated aqueous sodium bicarbonate solution (50 mL) and with saturated brine (50 mL) each three times. The aqueous layer was extracted with 50 mL of diethyl ether three times, combined with the
20 previously obtained ether layer. The ether layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:5) to give alcohol Compound 6 (1.67 g, 84%) as a colorless oil.

25 $[\alpha]_D^{20}$ 11.18 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.22 (s, 9H), 2.09 (d, 1H, J= 7.6 Hz), 4.25 (dd, 1H, J= 4.8, 12.4 Hz), 4.33 (dd, 1H, J= 3.2, 12.4 Hz), 4.37 (d, 1H, J= 7.6 Hz), 4.55 (d, 1H, J= 11.6 Hz), 4.73 (ddd, 1H, J= 1.6,

3.2, 4.3 Hz), 4.74 (d, 1H, J= 11.6 Hz), 5.10 (s, 1H), 5.26 (s, 1H), 5.54 (t, 1H, J= 1.6 Hz), 7.33 (m, 5H).

(6) Synthesis of benzyl 5-O-pivaloyl-2-methoxymethyl-3-deoxy-3-C-methylene- α -D-xylofuranose (Compound 7)

5 Compound 6 (1.0 g, 3.13 mmol) was dissolved in dichloromethane (25 mL), to which diisopropylethylamine (1.24 g, 9.61 mmol) and chloromethyl ethyl ether (1.29 g, 16.0 mmol) were added dropwise at 0°C. Tetrabutylammonium iodide (360 mg, 975 μ mol) was added to the reaction mixture
10 and then the mixture was stirred for 14 hours at room temperature in a dark. After the completion of the reaction, the reaction mixture was diluted with diethyl ether (150 mL) and washed with saturated aqueous ammonium chloride solution (25 mL) and with saturated brine (25 mL),
15 each three times. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:9) to give Compound 7 (1.01 g, 88%) as a colorless oil.

20 ^1H NMR (400 MHz, CDCl_3) δ 1.23 (s, 9H), 3.35 (s, 3H), 4.18 (dd, 1H, J= 6.4, 11.2 Hz), 4.22 (dd, 1H, J= 5.2, 11.2 Hz), 4.37 (s, 1H), 4.55 (d, 1H, J= 12.0 Hz), 4.60 (d, 1H, J= 6.8 Hz), 4.69 (ddd, 1H, J= 1.6, 5.2, 6.4 Hz), 4.75 (d, 1H, J= 12.0 Hz), 4.76 (d, 1H, J= 6.8 Hz), 5.21 (s, 1H), 5.36 (s,
25 1H), 5.46 (d, 1H, J= 1.6 Hz), 7.33 (m, 5H).

(7) Synthesis of benzyl 5-O-pivaloyl-2-methoxymethyl-3-deoxy-3-C-hydroxymethyl- α -D-xylo-pentofuranose (Compound 8)

Compound 7 (2.0 g, 5.49 mmol) was dissolved in THF

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(20 mL), cooled to 0°C, and a THF solution of 0.5M 9-BBN (9-borabicyclo[3,3,1]nonane) (20 mL, 10.0 mmol) was added dropwise. The reaction mixture was heated to 50°C, stirred for 3 hours and cooled to 0°C. To the mixture, 3.0M sodium hydroxide solution (6.4 mL, 19.2 mmol) and 30% hydrogen peroxide solution (12.8 mL) were added, followed by stirring vigorously for 2 hours at room temperature. The mixture was diluted with ethyl acetate (200 mL) and washed with water (50 mL), 5% aqueous sodium sulfite solution (50 mL) and with brine (50 mL), each three times. The thus obtained aqueous layer was extracted with 50 mL of diethyl ether three times. The ether layer was combined with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The thus obtained residue was purified by silica gel chromatography (ethyl acetate/hexane 1:3) to give Compound 8 (1.78 g, 85%) as a colorless oil.

[α]_D²⁰ 7.06 (c 1.70, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.22 (s, 9H), 2.34 (t, 1H, J= 6.0 Hz), 2.89 (tt, 1H, J= 6.0, 8.4 Hz), 3.37 (s, 3H), 3.86 (dt, 1H, J= 6.0, 11.2 Hz), 3.88 (ddd, 1H, J= 6.0, 8.4, 11.2 Hz), 4.19 (dd, 1H, J= 7.2, 11.6 Hz), 4.20 (d, 1H, J= 6.0 Hz), 4.23 (dd, 1H, J= 5.6, 11.6 Hz), 4.38 (dd, 1H, J= 5.6, 7.2, 8.4 Hz), 4.50 (d, 1H, J= 12.0 Hz), 4.66 (s, 2H), 4.73 (d, 1H, J= 12.0 Hz), 5.15 (s, 1H), 7.34 (m, 5H).

(8) Synthesis of benzyl 5-O-pivaloyl-2-methoxymethyl-3-deoxy-3-C-(tert-butyldimethylsilyloxymethyl)- α -D-xylo-pentofuranose (Compound 9)

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Compound 8 (2.97 g, 7.77 mmol) was dissolved in DMF (30 mL), to which solution imidazole (1.06 g, 15.6 mmol) and TBDMSCl (tert-butyldimethylsilyl chloride) (1.76 g, 11.7 mmol) were added at room temperature. The reaction mixture was stirred for 3 hours at room temperature, diluted with diethyl ether (200 mL) and washed with water (25 mL) and with saturated brine (25 mL), each three times. The thus obtained aqueous layer was extracted with 25 mL of diethyl ether three times. The ether layer was combined with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:9) to give Compound 9 (3.82 g, 99%) as a colorless oil.

15 $[\alpha]^{20}_D$ 7.65 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.18 (s, 9H), 2.80 (qt, 1H, J = 4.8, 6.8, 8.8 Hz), 3.28 (s, 3H), 3.70 (dd, 1H, J = 6.8, 10.0 Hz), 3.76 (dd, 1H, J = 8.8, 10.0 Hz), 4.07 (d, 1H, J = 4.8 Hz), 4.09 (dd, 1H, J = 7.4, 12.0 Hz), 4.13 (dd, 1H, J = 4.8, 12.0 Hz), 4.69 (d, 1H, J = 12.0 Hz), 5.10 (s, 1H), 7.28 (m, 5H); HREIMS $\text{C}_{25}\text{H}_{41}\text{O}_6\text{Si}$ ($\text{M}^+ - \text{OCH}_3$) calcd. 465.2673, found 465.2666.

(9) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3-methoxymethyloxy-6-O-pivaloyl-hex-1-en-5-ol (Compound 10)

Compound 9 (3.98 g, 8.02 mmol) was dissolved in ethanol (40 mL), and $\text{Pd}(\text{OH})_2$ (400 mg) was added, followed by stirring under hydrogen atmosphere for 12 hours at room

temperature for catalytic reduction. The reaction mixture was filtered through CELITE, and the filtrate was concentrated to give hemiacetal compound as a colorless oil which was subjected to the next reaction without further purification.

Methyltriphosponium bromide (10.9 g, 30.5 mL) was dissolved in THF (50 mL), cooled to 0°C under argon atmosphere, and 1.0 M LiHMDS (lithium bis(trimethylsilyl)amide) in THF (29 mL, 29.0 mmol) was added dropwise. The mixture was stirred at room temperature for 40 min. and then cooled again to 0°C when the color of the mixture was changed to yellow, followed by the addition of a THF solution of the hemiacetal (20 mL). The reaction mixture was stirred for 40 min. at 0°C, then MeOH (5 mL) was added. The mixture was diluted with diethyl ether (300 mL) and washed with saturated aqueous ammonium chloride solution (50 mL) and with saturated brine (50 mL), each three times. The organic layer was collected. The aqueous layer was extracted with 50 mL of diethyl ether three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:6) to give olefin Compound 10 (2.57 g, 79%) as a colorless oil.

$[\alpha]_D^{20}$ -5.63 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.21 (s, 9H), 2.74 (ddt, 1H, J= 4.4, 7.2, 8.0 Hz), 3.40 (s, 3H), 3.54 (d, 1H,

J= 5.6 Hz), 3.82 (dd, 1H, J= 4.4, 10.4 Hz), 3.90 (dd, 1H, J= 4.8, 5.6, 7.2 Hz), 4.40 (t, 1H, J= 8.0 Hz), 4.58 (d, 1H, J= 6.4 Hz), 4.72 (d, 1H, J= 6.4 Hz), 5.30 (dd, 1H, J= 1.2, 16.8 Hz), 5.33 (dd, 1H, J= 1.2, 10.4 Hz), 5.70 (ddd, 1H, J= 8.0, 10.4, 16.8 Hz); HREIMS $C_{19}H_{37}O_5Si$ (M^+-OCH_3) calcd. 373.2411, found 373.2421.

(10) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3-methoxymethyloxy-hex-1-en-5,6-diol (Compound 11)

10 Compound 10 (3.20 g, 7.92 mmol) was dissolved in dichloromethane (50 mL), and 1.0M DIBAL (diisobutyl aluminum hydride) in toluene (19.8 mL, 19.8 mmol) was added dropwise over 30 min. After 10 min., methanol (1 mL) and saturated aqueous ammonium chloride solution (1 mL) were
15 added to the reaction mixture, which was then diluted with diethyl ether (250 mL) and filtered through CELITE. The filtrate was washed with a saturated aqueous ammonium chloride solution (50 mL) and with saturated brine (50 mL), each three times. The organic layer was collected. The
20 aqueous layer was extracted with 25 mL of diethyl ether three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl
25 acetate/hexane 2:3) to give diol Compound 11 (2.12 g, 84%) as a colorless oil.

$[\alpha]^{20}_D$ -6.89 (c 1.00, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.77 (ddt, 1H, J= 4.8,

6.5, 8.0 Hz), 2.67 (dd, 1H, J= 4.8, 8.4 Hz), 3.40(s, 3H),
3.52 (d, 1H, J= 6.0 Hz), 3.70 (m, 1H), 3.83 (d, 1H, J= 4.8
Hz), 4.14 (m, 1H), 4.30 (t, 1H, J= 8.0 Hz), 4.57 (d, 1H, J=
6.8 Hz), 4.71 (d, 1H, J= 6.8 Hz), 5.29 (d, 1H, J= 16.8 Hz),
5 5.32 (dd, 1H, J= 10.0 Hz), 5.69 (ddd, 1H, J= 8.0, 10.0,
16.8 Hz); HREIMS $C_{14}H_{29}O_4Si$ (M^+-OCH_3) calcd. 289.1835, found
289.1838.

(11) Synthesis of 3S,4R,5R-4-(tert-
butyldimethylsilyloxymethyl)-3-methoxymethyloxy-hex-1-en-
10 5,6-epoxide (Compound 12)

Compound 11 (3.20 g, 11.6 mmol) was dissolved in
dichloromethane (40 mL), mixed with DMAP (4-
(dimethylamino)pyridine) (2.84 g, 23.4 mmol), cooled to 0°C
and vigorously stirred. To the mixture, 2-
15 mesitylenesulfonyl chloride (3.80 g, 17.4 mmol) was slowly
added, followed by stirring at that temperature for 4
hours. The reaction mixture was diluted with diethyl ether
(200 mL) and washed with water (25 mL) and with saturated
brine (25 mL), each three times. The aqueous layer was
20 extracted with 25 mL of diethyl ether three times. The
ether layers were combined with the previously obtained
ether layer, dried over magnesium sulfate, filtered and
concentrated to give a sulfonate, which was used to the
next step without further purification.

25 The sulfonate was dissolved in THF (50 mL), cooled to
-78°C, 1.0 M LiHMDS in THF (2.5 mL, 2.5 mmol) was added
dropwise. After stirring for 20 min. at that temperature,
the mixture was warmed to 0°C and stirred for further 20

min. The reaction mixture was diluted with diethyl ether (200 mL), washed with a saturated aqueous ammonium chloride solution (25 mL) and with saturated brine (25 mL), each three times. The aqueous layer was extracted with 25 mL of diethyl ether three time. The ether layers were combined with the previously obtained diethyl ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give epoxy Compound 12 (3.01 g, 86%) as a colorless oil.

$[\alpha]_D^{20}$ -7.90 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.26 (dddd, 1H, J= 3.4, 4.0, 5.2, 7.2 Hz), 2.62 (dd, 1H, J= 2.8, 5.2 Hz), 2.87 (t, 1H, J= 5.2 Hz), 3.04 (td, 1H, J= 2.8, 3.4, 5.2 Hz), 3.35 (s, 3H), 3.70 (dd, 1H, J= 4.0, 10.0 Hz), 3.82 (dd, 1H, J= 5.2, 10.0 Hz), 4.31 (t, 1H, J= 7.2 Hz), 4.51 (d, 1H, J= 6.4 Hz), 4.68 (d, 1H, J= 6.4 Hz), 5.24 (d, 1H, J= 10.2 Hz), 5.25 (d, 1H, J= 17.2 Hz), 5.70 (ddd, 1H, J= 7.2, 10.0, 17.2 Hz); HREIMS $\text{C}_{14}\text{H}_{27}\text{O}_3\text{Si}$ ($\text{M}^+ - \text{OCH}_3$) calcd. 271.1729, found 271.1732.

(12) Synthesis of 3S,4R,5R-4-(tert-butyltrimethylsilyloxymethyl)-3-methoxymethyloxy-8-trimethylsilyl-oct-1-en-7-yn-5-ol (Compound 13)

Ethynyltrimethylsilane (3.88 g, 39.6 mmol) was dissolved in THF (100 mL), cooled to 0°C . 1.54M n-Butyl lithium-hexane (22.7 mL, 36.0 mmol) was slowly added. The mixture was stirred at that temperature for 15 min., then cooled to -78°C . A solution of Compound 12 (3.01 g, 9.97

mmol) in THF (20 mL) and boron trifluoride diethyl ether complex (1.70 g, 12.0 mmol) were added. The mixture was warmed to room temperature, stirred for 40 min., diluted with diethyl ether (300 mL) and washed with a saturated aqueous ammonium chloride solution (50 mL) and with saturated brine (50 mL), each three times. The aqueous layer was extracted with diethyl ether (50 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give enyne Compound 13 (3.20 g, 80%) as a colorless oil.

$[\alpha]_D^{20}$ -7.14 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.11 (s, 9H), 0.87 (s, 9H), 1.93 (ddt, 1H, J= 4.0, 5.6, 8.0 Hz), 2.46 (dd, 1H, J= 8.0, 16.8 Hz), 2.63 (dd, 1H, J= 6.4, 16.8 Hz), 3.38 (s, 3H), 3.60 (d, 1H, J= 5.6 Hz), 3.81 (dd, 1H, J= 4.0, 10.0 Hz), 3.92 (dd, 1H, J= 5.6, 10.8 Hz), 4.21 (ddt, 1H, J= 5.6, 6.4, 8.0 Hz), 4.44 (t, 1H, J= 8.0 Hz), 4.58 (d, 1H, J= 6.4 Hz), 4.70 (d, 1H, J= 6.4 Hz), 5.28 (d, 1H, J= 17.2 Hz), 5.29 (d, 1H, J= 10.8 Hz), 5.71 (td, 1H, J= 8.0, 10.8, 17.2 Hz).

(13) Synthesis of 3S,4R,5R-4-hydroxymethyl-3-methoxymethyloxy-oct-1-en-7-yn-5-ol (Compound 14)

Compound 13 (3.20 g, 8.0 mmol) was dissolved in THF (45 mL), cooled to 0°C, and 1.0M TBAF (tetrabutylammonium fluoride) in THF (17.6 mL, 17.6 mmol) was added. The reaction mixture was warmed to room temperature, stirred for further 1 hour, diluted with ethyl acetate (200 mL) and

washed with a saturated aqueous ammonium chloride solution (25 mL) and with saturated brine (25 mL), each three times. The aqueous layer was extracted with ethyl acetate (25 mL) three times. The ethylacetate layers were combined with
5 the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 2:3) to give diol Compound 14 (1.69 g, 99%) as a colorless oil.

10 $[\alpha]_D^{20}$ -11.15 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.86 (ddt, 1H, J= 3.2, 4.8, 7.2 Hz), 2.05 (t, 1H, J= 2.8 Hz), 2.50 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 2.60 (bs, 1H), 2.63 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 3.32 (d, 1H, J= 4.4 Hz), 3.34 (s, 3H), 3.83 (dd, 1H, J= 4.8, 11.2 Hz), 4.00 (dd, 1H, J= 4.8, 11.2 Hz), 4.30 (ddt, 1H, J= 3.2, 4.4, 6.8 Hz), 4.44
15 (tt, 1H, J= 1.2, 7.2 Hz), 4.61 (d, 1H, J= 6.8 Hz), 4.70 (d, 1H, J= 6.8 Hz), 5.33 (dt, 1H, J= 1.2, 10.4 Hz), 5.35 (d, 1H, J= 1.2, 17.2 Hz), 5.71 (ddd, 1H, J=7.2, 10.4, 17.2 Hz).
(14) Synthesis of 3S,4R,5R-4-pivaloyloxymethyl-3-methoxymethyloxy-oct-1-en-7-yn-5-ol (Compound 15)
20

Compound 14 (1.62 g, 7.57 mmol) was dissolved in pyridine (1.7 mL) and dichloromethane (6.8 mL) and cooled to 0°C. To the solution, trimethylacetyl chloride (1.08 g, 8.96 mmol) was added dropwise over 30 min., and stirred at
25 the same temperature for 1 hour. The reaction mixture was warmed to room temperature, stirred for 4 hours, diluted with diethyl ether (100 mL) and washed with saturated aqueous ammonium chloride solution (20 mL) and with

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saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give alcohol Compound 15 (1.92 g, 85%) as a colorless oil.

$[\alpha]_D^{20}$ -10.05 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.22 (s, 9H), 2.03 (t, 1H, J = 8.0 Hz), 2.46 (ddt, 1H, J = 2.4, 4.8, 5.6 Hz), 2.46 (ddd, 1H, J = 2.4, 7.6, 16.8 Hz), 2.58 (ddd, 1H, J = 2.4, 6.4, 16.8 Hz), 3.10 (d, 1H, J = 2.4 Hz), 3.39 (s, 3H), 4.26 (ddt, 1H, J = 2.4, 6.4, 7.6 Hz), 4.29 (dd, 1H, J = 5.6, 11.6 Hz), 4.33 (dd, 1H, J = 5.6, 11.6 Hz), 4.40 (ddt, 1H, J = 1.2, 4.8, 6.8 Hz), 4.44 (t, 1H, J = 8.0 Hz), 4.57 (d, 1H, J = 7.2 Hz), 4.70 (d, 1H, J = 7.2 Hz), 5.31 (dt, 1H, J = 1.2, 17.6 Hz), 5.34 (d, 1H, J = 1.2, 10.4 Hz), 5.71 (ddd, 1H, J = 6.8, 10.4, 17.6 Hz).

(15) Synthesis of 3S,4R,5R-4-pivaloyloxymethyl-oct-1-en-7-yn-3,5-diol (Compound 16)

Compound 15 (2.10 g, 7.05 mmol) was dissolved in tert-butyl alcohol (60 mL). Pyridinium p-toluenesulfonate (17.6 g, 70.0 mmol) was added. The mixture was refluxed for 12 hours. The reaction mixture was cooled to room temperature and then concentrated. The residue was diluted with diethyl ether (200 mL) and washed with saturated sodium bicarbonate solution (20 mL) and with saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The

ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:3) to give diol

5 Compound 16 (1.33 g, 74%) as a colorless oil.

[α]_D²⁰ 1.75 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.22 (s, 9H), 2.05 (t, 1H, J= 2.4 Hz), 2.06 (dddd, 1H, J= 2.4, 4.4, 5.6, 6.8 Hz), 2.43 (ddd, 1H, J= 2.4, 7.2, 16.8 Hz), 2.57 (ddd, 1H, J= 2.4, 7.2, 16.8 Hz), 2.73 (d, 1H, J= 4.4 Hz), 3.07 (d, 1H, J= 2.4 Hz), 4.24 (tt, 1H, J= 2.4, 7.2 Hz), 4.31 (dd, 1H, J= 5.6, 11.6 Hz), 4.43 (dd, 1H, J= 6.8, 11.6 Hz), 4.45 (ddt, 1H, J= 1.2, 4.4, 5.6 Hz), 5.28 (dt, 1H, J= 1.2, 10.4 Hz), 5.28 (dt, 1H, J= 1.2, 10.4 Hz), 5.40 (d, 1H, J= 1.2, 16.8 Hz), 5.92 (ddd, 1H, J= 5.6, 10.4, 16.8 Hz).

(16) Synthesis of 3S,4R,5R-4-pivaloyloxymethyl-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 17)

Compound 16 (1.31 g, 5.16 mmol) was dissolved in dichloromethane (25 mL), cooled to 0°C, and 2,6-lutidine (2.21 g, 20.6 mmol) and TBDMSOTf (tert-butyldimethylsilyltriflate) (4.09 g, 15.5 mmol) were added. The reaction mixture was stirred for 2 hours at the same temperature, diluted with diethyl ether (150 mL) and washed with a saturated aqueous sodium bicarbonate solution (20 mL) and with saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium

sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:40) to give silyl ether Compound 17 (2.47 g, 99%) as a colorless oil.

5 $[\alpha]_D^{20}$ -0.37 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.20 (s, 9H), 1.98 (t, 1H, J = 2.4 Hz), 2.19 (dq, 1H, J = 4.0, 6.0 Hz), 2.45 (ddd, 1H, J = 2.4, 4.8, 16.4 Hz), 2.54 (ddd, 1H, J = 2.4, 7.2, 16.4 Hz), 3.99 (dd, 1H, J = 6.0, 12.0 Hz), 4.16 (ddd, 1H, J = 4.0, 4.8, 7.2 Hz), 4.17 (dd, 1H, J = 6.0, 7.6 Hz), 4.25 (dd, 1H, J = 6.0, 12.0 Hz), 5.09 (d, 1H, J = 10.0 Hz), 5.16 (d, 1H, J = 17.2 Hz), 5.84 (ddd, 1H, J = 7.6, 10.0, 17.2 Hz); HREIMS $\text{C}_{22}\text{H}_{41}\text{O}_4\text{Si}_2$ (M^+ -t-Bu) calcd. 425.2543, found 425.2543

15 (17) Synthesis of 3S,4R,5R-4-hydroxymethyl-3,5-di-(tert-butyl)dimethylsilyloxy)-oct-1-en-7-yne (Compound 18)

Compound 17 (2.47 g, 5.12 mmol) was dissolved in dichloromethane (20 mL) and cooled to -78°C . 1.0M Diisobutyl aluminium hydride in toluene (7.7 mL, 7.70 mmol) was added dropwise over 30 min. The mixture was stirred at the same temperature for 10 min. Methanol (1 mL) and saturated aqueous ammonium chloride solution (1 mL) were added, and diluted with diethyl ether (200 mL). The mixture was filtered through CELITE. The filtrate was washed with saturated aqueous ammonium chloride solution (20 mL) and with saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The ether layers were combined with the

previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:10) to give alcohol Compound 18 (1.96 g, 5 96%) as a colorless oil.

[α]_D²⁰ 0.11 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.90 (s, 18H), 2.01 (t, 1H, J= 2.8 Hz), 2.09 (ddt, 1H, J= 2.0, 4.8, 7.2 Hz), 2.46 (ddd, 1H, J= 2.8, 4.8, 16.8 Hz), 2.51 (ddd, 10 1H, J= 2.8, 6.8, 16.8 Hz), 3.07 (dd, 1H, J= 4.8, 7.2 Hz), 3.72 (ddd, 1H, J= 4.8, 7.2, 12.4 Hz), 3.82 (dt, 1H, J = 7.2, 12.4 Hz), 4.08 (dt, 1H, J= 4.8, 6.8 Hz), 4.33 (dd, 1H, J= 6.0, 12.0 Hz), 5.20 (dt, 1H, J = 2.0, 10.4 Hz), 5.28 (dt, 1H, J = 2.0, 17.2 Hz), 5.84 (ddd, 1H, J= 7.2, 10.4, 15 17.2 Hz); HREIMS C₂₁H₄₂O₃Si₂ (M⁺) calcd. 398.2672, found 398.2669.

(18) Synthesis of 3S,4R,5R-4-(tert-butyl dimethylsilyloxymethyl)-3,5-di-(tert-butyl dimethylsilyloxy)-oct-1-en-7-yne (Compound 19)

20 Compound 18 (40.0 mg, 101 μ mol) was dissolved in DMF (2.0 mL), and imidazole (13.6 mg, 200 μ mol) and TBDMSCl (tert-butyl dimethylsilyl chloride) (22.6 mg, 150 μ L) were added at room temperature. The mixture was stirred for 3 hours. The reaction mixture was diluted with diethyl ether 25 (20 mL) and washed with water (5 mL) and with saturated brine (5 mL), each three times. The aqueous layer was extracted with diethyl ether (5 mL) three times. The ether layers were combined with the previously obtained ether

layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:50) to give silyl ether Compound 19 (46.0 mg, 88%) as a colorless oil.

5 $[\alpha]^{20}_D$ 0.59 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 0.90 (s, 18H), 1.93 (t, 1H, J = 2.8 Hz), 2.00 (ddt, 1H, J = 5.2, 5.6, 6.4 Hz), 2.44 (ddd, 1H, J = 2.8, 5.6, 16.8 Hz), 2.57 (ddd, 1H, J = 2.8, 5.6, 16.8 Hz), 3.56 (dd, 1H, J = 6.0, 10.0 Hz), 3.81 (dd, 1H, J = 6.0, 10.0 Hz), 4.09 (dt, 1H, J = 4.8, 5.6 Hz), 4.30 (ddt, 1H, J = 1.2, 5.2, 6.8 Hz), 5.03 (dt, 1H, J = 1.2, 9.6 Hz), 5.11 (dt, 1H, J = 1.2, 17.2 Hz), 5.92 (ddd, 1H, J = 6.8, 9.6, 17.2 Hz).

10 (19) Synthesis of (3S,4R,5R-4-cyanomethyl-3,5-di-(tert-butyl)dimethylsilyloxy)-oct-1-en-7-yne (Compound 20)

15 Compound 18 (314 mg, 789 μmol) was dissolved in dichloromethane, and DMAP (dimethylaminopyridine) (372 mg, 3.04 mmol) was added, followed by cooling to 0°C. 2-Mesitylenesulfonyl chloride (582 mg, 2.66 mmol) was added with vigorous stirring. The mixture was stirred for 12 hours at the same temperature. The reaction mixture was diluted with diethyl ether (100 mL) and washed with water (15 mL) and with saturated brine (15 mL), each three times. The aqueous layer was extracted with diethyl ether (15 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The thus obtained residue was subjected to the next step without further

purification.

The sulfon ester was dissolved in DMSO (dimethylsulfoxide) (5.0 mL), and sodium cyanide (78.0 mg, 1.59 mmol) was added, followed by stirring at 70°C for 2 hours. The reaction mixture was cooled to room temperature, diluted with diethyl ether (100 mL) and washed with water (15 mL) and with saturated brine (15 mL), each three times. The aqueous layer was extracted with diethyl ether (15 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:20) to give nitrile Compound 20 (263 mg, 82%) as a colorless oil.

[α]_D²⁰ -0.44 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.12 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 2.03 (t, 1H, J= 2.8 Hz), 2.29 (tt, 1H, J= 6.0, 6.8 Hz), 2.36 (dd, 1H, J= 6.0, 16.4 Hz), 2.46 (ddd, 1H, J= 2.8, 4.4, 16.8 Hz), 2.48 (dd, 1H, J= 6.0, 16.4 Hz), 2.52 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 4.04 (dt, 1H, J = 4.4, 6.8 Hz), 4.20 (ddt, 1H, J= 1.2, 6.4, 6.8 Hz), 5.24 (dt, 1H, J= 1.2, 10.4 Hz), 5.31 (dt, 1H, J = 1.2, 16.8 Hz), 5.82 (ddd, 1H, J= 6.4, 10.4, 16.8 Hz).

(20) Synthesis of 3S,4R,5R-3,5-di-(tert-butyltrimethylsilyloxy)-4-(2'-ethanal)-oct-1-en-7-yne (Compound 21)

Compound 20 (184 mg, 452 μ mol) was dissolved in dichloromethane (2.0 mL), cooled to -78°C, and 1.0M

10055481.022702
diisobutyl aluminium hydride in toluene (530 μ L, 530 μ mol) was added over 10 min., followed by stirring for 1 hour at that temperature. Methanol (1 mL) and a saturated aqueous ammonium chloride solution (1 mL) were added to the
5 reaction mixture, which was then diluted with diethyl ether (100 mL). The mixture was filtered through CELITE. The filtrate was washed with saturated aqueous ammonium chloride solution (10 mL) and saturated brine (10 mL), each three times. The aqueous layer was extracted with diethyl
10 ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:20) to give aldehyde Compound 21 (157 mg,
15 85%) as a colorless oil.

$[\alpha]_D^{20}$ 0.77 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 2.04 (t, 1H, J = 2.8 Hz), 2.37 (ddd, 1H, J = 2.8, 6.0, 16.8 Hz), 2.40 (ddd, 1H, J = 2.8, 6.4, 17.2
20 Hz), 2.42 (ddd, 1H, J = 1.6, 7.2, 17.2 Hz), 2.44 (ddd, 1H, J = 2.8, 6.0, 16.8 Hz), 2.68 (ddd, 1H, J = 5.2, 6.4 Hz), 3.84 (dt, 1H, J = 5.2, 6.0 Hz), 4.23 (ddt, 1H, J = 1.6, 6.4, 6.8 Hz), 5.18 (dt, 1H, J = 1.6, 10.0 Hz), 5.21 (dt, 1H, J = 1.6, 16.0 Hz), 5.73 (ddd, 1H, J = 6.8, 10.0, 16.8 Hz); HREIMS
25 $\text{C}_{22}\text{H}_{42}\text{O}_3\text{Si}_2$ (M^+) calcd. 410.2673, found 410.2667.

(21) Synthesis of 3S,4R,5R-4-(2'-hydroxyethyl)-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 22)

Compound 21 (157 mg, 383 μ mol) was dissolved in

methanol (2.0 mL), cooled to 0°C, and sodium borohydride (28.0 mg, 741 µmol) was added, followed by stirring at the same temperature for 30 min. The reaction mixture was warmed to room temperature, diluted with diethyl ether (100 mL) and washed with water (10 mL) and with saturated brine (10 mL), each three times. The aqueous layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated.

10 The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give alcohol Compound 22 (129 mg, 82%) as a colorless oil.

[α]_D²⁰ 1.40 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.08 (s, 6H), 0.10 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.67 (m, 2H), 2.03 (t, 1H, J= 2.8 Hz), 2.29 (tt, 1H, J= 6.0, 6.8 Hz), 2.36 (dd, 1H, J= 6.0, 16.4 Hz), 2.01 (t, 1H, J= 2.4 Hz), 2.04 (ddt, 1H, J= 4.8, 5.6, 7.2 Hz), 2.41 (ddd, 1H, J= 2.4, 5.6, 17.2 Hz), 2.45 (ddd, 1H, J= 2.4, 5.6, 17.2 Hz), 2.93 (bs, 1H), 3.65 (m, 2H), 3.85 (q, 1H, J = 5.6 Hz), 4.27 (ddt, 1H, J= 1.2, 4.8, 6.8 Hz), 5.18 (dt, 1H, J= 1.2, 10.8 Hz), 5.21 (dt, 1H, J = 1.2, 17.6 Hz), 5.86 (ddd, 1H, J= 6.8, 10.8, 17.6 Hz).

(22) Synthesis of 3S,4R,5R-4-(2'-tert-butylldimethylsilyloxyethyl)-3,5-di-(tert-butylldimethylsilyloxy)-oct-1-en-7-yne (Compound 23)

From Compound 22 (60.0 mg, 146 µmol), silyl ether Compound 23 (59.0 mg, 78%) was obtained according to the same procedure of Compound 19.

10065481.022702
[α]²⁰_D 0.90 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.90 (s, 3H), 0.89 (s, 27H), 1.55 (m, 2H), 1.84 (ddt, 1H, J= 3.6, 5.2, 6.4 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.36 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 2.41 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 3.57 (dt, 1H, J= 6.4, 8.4 Hz), 3.69 (dd, 1H, J= 6.4, 10.0 Hz), 4.01 (dt, 1H, J= 3.6, 6.4 Hz), 4.13 (t, 1H, J = 6.4 Hz), 5.11 (d, 1H, J= 10.4 Hz), 5.17 (d, 1H, J= 17.2 Hz), 5.82 (ddd, 1H, J= 6.4, 10.4, 17.2 Hz).

10 (23) Synthesis of 3S,4R,5R-3,5-di-(tert-butylldimethylsilyloxy)-4-ethyl-oct-1-en-7-yne (Compound 24)

Compound 22 (100 mg, 243 μ mol) was dissolved in dichloromethane (2.0 mL), and DMAP (74.0 mg, 606 μ mol) was added. The mixture was cooled to 0°C. 2-Mesitylene
15 sulfonyl chloride (106 mg, 485 μ mol) was slowly added with vigorous stirring, and then stirred for 12 hours at the same temperature. The reaction mixture was diluted with diethyl ether (100 mL) and washed with water (10 mL) and with saturated brine (10 mL), each three times. The
20 aqueous layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The thus obtained sulfon ester was subjected to the next step without further
25 purification.

The sulfon ester was dissolved in diethyl ether (2.0 mL), cooled to 0°C. LAH (lithium aluminium hydride) (46.0 mg, 1.20 μ mol) was slowly added. The mixture was stirred

at the same temperature for 1 hour and at room temperature for further 3 hours. The reaction mixture was cooled to 0°C, and ethyl acetate (1 mL) and saturated aqueous ammonium chloride solution (1 mL) were added, followed by
5 diluting with diethyl ether (100 mL). The mixture was filtered through CELITE. The filtrate was washed with saturated aqueous ammonium chloride solution (10 mL) and saturated brine (10 mL), each three times. The aqueous
10 layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:100) to give enyne Compound 24 (77.0 mg, 80%) as a colorless oil.
15 $[\alpha]_D^{20}$ 1.95 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 18H), 0.94 (t, 3H, J= 7.6 Hz), 1.36 (m, 2H), 1.68 (ddt, 1H, J= 3.6, 5.2, 6.0 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.39 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 2.42 (ddd, 1H, J= 2.8, 6.4, 16.8
20 Hz), 4.01 (dt, 1H, J= 3.6, 6.4 Hz), 4.14 (ddt, 1H, J= 1.2, 5.2, 7.2 Hz), 5.08 (dt, 1H, J= 1.2, 10.4 Hz), 5.14 (dt, 1H, J= 1.2, 16.8 Hz), 5.86 (ddd, 1H, J= 7.2, 10.4, 16.8 Hz).
(24) Synthesis of 3S,4R,5R-3,5-di-(tert-butyltrimethylsilyloxy)-4-(2'-cyanoethyl)-oct-1-en-7-yne
25 (Compound 25)

From Compound 22 (129 mg, 313 μmol), nitrile Compound 25 (80.0 mg, 61%) was obtained as a colorless oil according to the same procedure of Compound 20.

20 220" F046900F
[α]_D²⁰ 1.40 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 3H), 0.08 (s, 6H), 0.10 (s, 3H), 0.90 (s, 18H), 1.73 (m, 2H), 1.96 (q, 1H, J= 6.4 Hz), 2.03 (t, 1H, J= 2.4 Hz), 2.38 (ddd, 1H, J= 2.4, 6.0, 16.8 Hz), 2.43 (ddd, 1H, J= 2.4, 4.8, 16.8 Hz), 2.50 (dt, 2H, J= 4.0, 8.4 Hz), 3.88 (dt, 1H, J= 4.8, 6.0 Hz), 4.18 (tt, 1H, J= 1.2, 6.4 Hz), 5.19 (dt, 1H, J = 1.2, 10.4 Hz), 5.25 (dt, 1H, J= 1.2, 17.2 Hz), 5.80 (ddd, 1H, J= 6.4, 10.4, 17.2 Hz) ; HREIMS C₂₃H₄₃O₂NSi₂ (M⁺) calcd. 421.2814, found 421.2812.

- 10 (25) Synthesis of 3S,4R,5R-3,5-di-(tert-butyltrimethylsilyloxy)-4-(3'-propanal)-oct-1-en-7-yne (Compound 26)

From the nitrile Compound 25 (80.0 mg, 190 μ mol), aldehyde Compound 26 (71.0 mg, 89%) was obtained as a colorless oil according to the same procedure of Compound 21.

15 [α]_D²⁰ 0.37 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.69 (m, 2H), 1.87 (ddt, 1H, J= 5.2, 5.6, 6.0 Hz), 1.87 (ddt, 1H, J= 5.2, 5.6, 6.0 Hz), 1.99 (t, 1H, J= 2.8 Hz), 2.40 (ddd, 1H, J= 2.8, 6.0, 17.2 Hz), 2.43 (ddd, 1H, J= 2.8, 6.0, 17.2 Hz), 2.57 (ddd, 1H, J= 2.0, 2.8, 6.0 Hz), 2.59 (ddd, 1H, J= 2.0, 3.2, 6.0 Hz), 3.94 (dt, 1H, J = 4.4, 6.0 Hz), 4.17 (ddt, 1H, J= 1.6, 5.6, 6.8 Hz), 5.14 (dt, 1H, J= 1.6, 10.4 Hz), 5.25 (dt, 1H, J= 1.6, 17.2 Hz), 5.80 (ddd, 1H, J= 6.8, 10.4, 17.2 Hz).

(26) Synthesis of 3S,4R,5R-4-(3'-hydroxypropyl)-3,5-di-(tert-butyltrimethylsilyloxy)-oct-1-en-7-yne (Compound 27)

From the aldehyde Compound 26 (71.0 mg, 167 μ mol), alcohol Compound 27 (70.0 mg, 98%) was obtained as a colorless oil according to the same procedure of Compound 22.

5 $[\alpha]^{20}_D$ 1.18 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.39 (m, 2H), 1.57 (bs, 1H), 1.66 (q, 1H, J = 6.4 Hz), 1.85 (ddt, 1H, J = 4.8, 5.2, 5.6 Hz), 1.98 (t, 1H, J = 2.8 Hz), 2.39 (ddd, 1H, J = 2.8, 6.4, 16.4 Hz), 2.43 (ddd, 1H, J = 2.8, 6.4, 16.4 Hz), 3.61 (t, 2H, J = 6.4 Hz), 3.97 (dt, 1H, J = 4.8, 6.4 Hz), 4.16 (ddt, 1H, J = 1.2, 5.6, 7.2 Hz), 5.12 (dt, 1H, J = 1.2, 9.6 Hz), 5.17 (dt, 1H, J = 1.6, 16.8 Hz), 5.84 (ddd, 1H, J = 7.2, 9.6, 16.8 Hz); HREIMS $\text{C}_{23}\text{H}_{46}\text{O}_3\text{Si}_2$ (M^+) calcd. 426.2985, found 426.2977.

15 (27) Synthesis of 3S,4R,5R-4-(3'-tert-butyltrimethylsilyloxypropyl)-3,5-di-(tert-butyltrimethylsilyloxy)-oct-1-en-7-yne (Compound 28)

From the alcohol Compound 27 (60.0 mg, 141 μ mol), silyl ether Compound 28 (63.0 mg, 83%) was obtained as a colorless oil according to the same procedure of Compound 23.

20 $[\alpha]^{20}_D$ 1.00 (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 27H), 1.32 (m, 2H), 1.56 (m, 2H), 1.75 (ddt, 1H, J = 4.0, 6.4, 6.8 Hz), 1.95 (t, 1H, J = 2.8 Hz), 2.38 (ddd, 1H, J = 2.8, 6.4, 16.8 Hz), 2.42 (ddd, 1H, J = 2.8, 6.4, 16.8 Hz), 3.56 (t, 2H, J = 6.8 Hz), 4.03 (dt, 1H, J = 3.6, 6.0 Hz), 4.12 (dd, 1H, J = 6.4, 7.6 Hz), 5.08 (d, 1H,

J= 10.0 Hz), 5.14 (d, 1H, J= 17.2 Hz), 5.84 (ddd, 1H, J= 7.6, 10.0, 17.2 Hz).

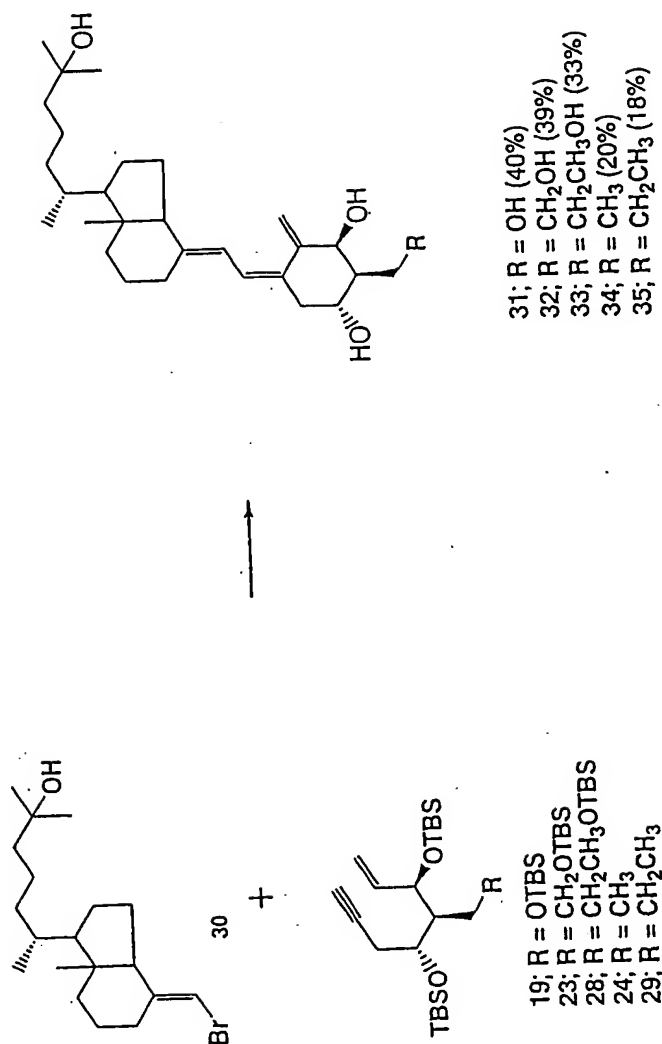
(28) Synthesis of 3S,4R,5R-3,5-di-(tert-butyltrimethylsilyloxy)-4-propyl-oct-1-en-7-yne (Compound 29)

From the alcohol Compound 27 (70.0 mg, 164 μ mol), enyne Compound 29 (54.0 mg, 80%) was obtained as a colorless oil according to the same procedure of Compound 24.

[α]_D²⁰ 2.24 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.02 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.87 (t, 3H, J= 7.2 Hz), 0.89 (s, 18H), 1.27 (m, 2H), 1.36 (m, 2H), 1.76 (ddt, 1H, J= 4.0, 5.2, 6.0 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.39 (ddd, 1H, J= 2.8, 6.4, 17.6 Hz), 2.41 (ddd, 1H, J= 2.8, 6.4, 17.6 Hz), 3.99 (dt, 1H, J= 4.0, 6.4 Hz), 4.12 (ddt, 1H, J= 1.2, 6.0, 8.0 Hz), 5.07 (dt, 1H, J= 1.2, 10.4 Hz), 5.13 (dt, 1H, J= 1.2, 17.2 Hz), 5.85 (ddd, 1H, J= 8.0, 10.4, 17.2 Hz).

(Example 2) Synthesis of vitamin D derivatives having a substituent at the 2 α -position.

Example 2 was done by the following reaction scheme:



(1) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol (Compound 31)

5 The silyl ether Compound 19 (20.0 mg, 39.1 μ mol) and a vinyl bromide 30 (20.0 mg, 58.0 μ mol), which corresponds to a compound of Formula (I) in which R¹ is a 4-hydroxy-4-methylpentyl group, were dissolved in triethylamine/toluene (3:1, 2.0 mL). Tris(dibenzylideneacetone)-dipalladium(0)-

chloroform addition product (4.0 mg, 3.86 μmol) and triphenylphosphine (10.0 mg, 38.1 μmol) were added. The mixture was stirred at room temperature for 15 min. and then refluxed for 2 hours. The reaction mixture was
5 filtered through silica gel; the filtrate was concentrated and roughly purified by thin layer chromatography (ethyl acetate/hexane 1:4) to give a protected derivative as a colorless solid. The crude protected body was subjected to the next step without further purification.

10 The protected derivative was dissolved in methanol (2.0 mL), cooled to 0°C and (+)-10-camphorsulfonic acid (10.0 mg, 43 μmol) was added. The mixture was stirred at the same temperature for 1 hour and then returned to room temperature, followed by stirring for further 12 hours.
15 The reaction mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium bicarbonate solution (1.0 mL) and saturated brine (1.0 mL), each three times. The aqueous layer was extracted with ethyl acetate (2 mL) three times. The ethylacetate layers were combined
20 with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by thin layer chromatography (ethyl acetate/hexane 1:4) to give Compound 31 (7.0 mg, 40%) as a colorless solid.

25 $[\alpha]^{20}_D$ 12.95 (c 0.0085, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.53 (s, 3H), 0.94 (d, 3H, J = 6.8 Hz), 2.31 (m, 2H), 2.67 (dd, 1H, J = 4.4, 12.8 Hz), 2.73 (bs, 1H), 2.84 (m, 1H), 4.01 (m, 2H), 4.24 (m, 1H), 4.47 (bs, 1H), 5.02 (d, 1H, J =

2.0 Hz), 5.30 (d, 1H, J= 2.0 Hz), 5.98 (d, 1H, J= 10.8 Hz),
6.45 (d, 1H, J= 10.8 Hz) ; HREIMS $C_{28}H_{44}O_3$ ($M^+ - H_2O$) calcd.
428.3290, found 428.3287.

(2) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-
5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol
(Compound 32)

From the silyl ether Compound 23 (25.0 mg, 47.5
 μmol), Compound 32 (8.5 mg, 39%) was obtained as a
colorless solid according to the same procedure of Compound
31.

$[\alpha]^{20}_D$ 13.85 (c 0.00722, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ
0.53 (s, 3H), 0.94 (d, 3H, J= 6.4 Hz), 2.26 (dd, 1H, J=
8.0, 12.8 Hz), 2.53 (bs, 1H), 2.66 (dd, 1H, J= 4.0, 13.2
Hz), 2.83 (m, 1H), 3.79 (m, 2H), 3.94 (m, 1H), 4.37 (d, 1H,
J= 2.0 Hz), 5.02 (d, 1H, J= 1.2 Hz), 5.30 (bs, 1H), 6.01
(d, 1H, J= 10.8 Hz), 6.40 (d, 1H, J= 10.8 Hz) ; HREIMS
 $C_{29}H_{48}O_4$ (M^+) calcd. 460.3553, found 460.3557.

(3) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-
5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-
triol(Compound 33)

From the silyl ether Compound 28 (25.0 mg, 46.3
 μmol), Compound 33 (7.2 mg, 33%) was obtained as a
colorless solid according to the same procedure of Compound
31.

$[\alpha]^{20}_D$ 161.29 (c 0.00186, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ
0.53 (s, 3H), 0.94 (d, 3H, J= 6.4 Hz), 2.25 (dd, 1H, J=
8.4, 13.2 Hz), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m,
1H), 3.70 (t, 2H, J= 5.6 Hz), 3.90 (dt, 1H, J= 4.0, 8.0

Hz), 4.38 (d, 1H, J= 3.6 Hz), 5.00 (d, 1H, J= 1.6 Hz), 5.28 (d, 1H, J= 1.6 Hz), 6.00 (d, 1H, J= 11.2 Hz), 6.40 (d, 1H, J= 11.2 Hz).

(4) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-
5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol (Compound
34)

From the enyne Compound 24 (30.0 mg, 75.8 μ mol),
Compound 34 (6.8 mg, 20%) was obtained as a colorless solid
according to the same procedure of Compound 31.

¹H NMR (400 MHz, CDCl₃) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.0 Hz), 0.95 (t, 3H, J= 7.2 Hz), 2.24 (dd, 1H, J= 8.8, 12.8 Hz), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m, 1H), 3.89 (m, 1H), 4.37 (bs, 1H), 4.99 (d, 1H, J= 1.6 Hz), 5.27 (bs, 1H), 6.00 (d, 1H, J= 11.2 Hz), 6.40 (d, 1H, J= 11.2 Hz); HREIMS
C₂₉H₄₈O₃ (M⁺) calcd. 444.3603, found 460.3604.

(5) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-
5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol (Compound
35)

From the enyne Compound 29 (30.0 mg, 73.2 μ mol),
Compound 35 (6.2 mg, 18%) was obtained as a colorless solid
according to the same procedure of Compound 31.

¹H NMR (400 MHz, CDCl₃) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.4 Hz), 1.01 (t, 3H, J= 6.8 Hz), 2.24 (dd, 1H, J= 8.8, 12.4 Hz), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m, 1H), 3.89 (m, 1H), 4.39 (bs, 1H), 4.99 (d, 1H, J= 1.6 Hz), 5.27 (bs, 1H), 6.00 (d, 1H, J= 11.2 Hz), 6.40 (d, 1H, J= 11.2 Hz). ;
HREIMS C₃₀H₅₀O₃ (M⁺) calcd. 458.3760, found 458.3755.

(Test example 1) Assay for binding to vitamin D receptor (VDR)

5 Bovine thymus $1\alpha,25$ -dihydroxyvitamin D_3 receptor was purchased from YAMASA SHOYU KABUSHIKI KAISHA (lot.110431) and 1 ampule (approximately 25 mg) of the receptor was dissolved in 55 mL of 0.05 M phosphate 0.5M potassium buffer (pH 7.4) just before use. Ethanol solutions (50 μ l) of $1\alpha,25$ -dihydroxyvitamin D_3 and Compounds 31-35 of the present invention at various concentrations were prepared, 10 mixed with aliquots (500 μ l, 0.23 mg protein) of the receptor solution and pre-incubated at room temperature for 1 hour. To the resultant mixtures, [3 H]- $1\alpha,25$ -dihydroxyvitamin D_3 was added at the final concentration of 0.1 nM, followed by incubation overnight at 4°C.

15 The reaction mixtures were treated with dextran coated charcoal for 30 minutes at 4°C to separate the bound and free forms of [3 H]- $1\alpha,25$ -dihydroxyvitamin D_3 , and centrifuged at 3000 rpm for ten minutes. Each of the resultant supernatants (500 μ l) was mixed with ACS-II (9.5 20 ml) (AMERSHAM, England) for radioactivity measurement.

The binding properties of Compounds 31-35 of the present invention were expressed in relative values with that of $1\alpha,25$ -dihydroxyvitamin D_3 taken as 100. The results are shown in Table 1.

Table 1

Compound	Binding property
31	20
32	70
33	300
34	40
35	20

INDUSTRIAL APPLICABILITY

5 Vitamin D₃ derivatives represented by Formula (I), (II) and (III) of the present invention are novel compounds and may be useful as pharmaceutical agents. The compounds of the present invention may be useful as reagents for studying metabolism of active vitamin D₃, that is, 1 α ,25-dihydroxyvitamin D₃.